

Remarks

Claims 1-14 are pending in the subject application. Claims 1-14 are cancelled above and new claims 16 and 17 are provided. Support for new claims 16 and 17 is found throughout the application, and particularly at paragraphs 0023, 0037 and 0011. The application teaches that an elevated uric acid level is a causal factor for hypertension (paragraph 0037) and that hypertension can be treated by reducing uric acid levels (paragraph 0023). The application also teaches that a uric acid level of 6 mg/dl and above is associated with an increased risk of hypertension and should be reduced to below such level. An optimal uric acid level of 4 to 6 mg/dl is also taught (see paragraph 0023).

Cancelled claims 1, 5, 7 and 14 were rejected under 35 USC § 112, first paragraph, as not enabled for the prevention of hypertension. Applicants respectfully assert that new claims 16 and 17 obviate this basis for rejection. Claims 16 and 17 pertain to a method of lowering uric acid to treat a condition, the condition being hypertension. Applicants understand that the issue regarding enablement centers on the issue of prevention versus treatment to a condition such as hypertension. Applicants assert that the new claims 16 and 17 pertain to a method of treating hypertension which avoids this issue. Applicants respectfully request reconsideration of this 35 USC § 112, first paragraph, rejection.

Cancelled claims 1, 5, 7 and 14 were rejected under 35 USC § 112, first paragraph, as not enabled for any substances or compounds represented by xanthine oxidase inhibitors. Applicants respectfully assert that new claims 16 and 17 obviate this basis for rejection. Claim 16 is drafted to recite that hypertension is treated by reducing uric acid to below a certain level. It is a well-documented scientific fact that xanthine oxidase produces uric acid upon oxidation of xanthine. Compounds defined as xanthine oxidase inhibitors must inhibit the enzyme xanthine oxidase. There is no question that a xanthine oxidase inhibitor will lower uric acid levels in a subject. All xanthine oxidase

inhibitors are enabled for this purpose. Thus, since this is true, logically claim 16 is enabled for any xanthine oxidase inhibitor to reduce uric acid.

The office action cites to Miyamoto et al. to support the position that not all xanthine oxidase inhibitors will serve to lower blood pressure. This no longer should be an issue in light of the wording in claim 16. It is true that the Miyamoto paper indicates variability amongst different xanthine oxidase inhibitors on lowering blood pressure in the SHR rat. However, careful analysis of Miyamoto's experimental shows that the variability is limited to specific rat model used and the short term focus on oxidant production, which do not correlate with what occurs in humans. Applicants present a Declaration from Dr. Richard Johnson (see attached) which further expounds upon why Miyamoto observed varying results and how Miyamoto failed to realize or consider that uric acid levels affect blood pressure. In sum, Miyamoto et al. adopted the flawed hypothesis that hypertension is caused by superoxide, an oxidant produced by xanthine oxidase and used a flawed rat model. It is known that superoxide produced by xanthine oxidase has a very short half-life of milliseconds. Not surprisingly, Miyamoto monitored blood pressure only over a very brief period of time, about 60 min (see Fig 6, Miyamoto et al.). Based on Miyamoto's theory that oxidants might affect blood pressure it makes empiric sense to only monitor for an hour or less (see paragraphs 3, 5 and 6 Johnson Declaration). However, Miyamoto's mechanistic theory of hypertension ultimately fails because the effect of xanthine oxidase inhibition in the SHR rat is not sustained; several studies have reported no effect on blood pressure when evaluated over days. This can be explained by the fact that the SHR rat becomes hypertensive by a genetic defect that is independent of uric acid levels. Therefore, the SHR rat model used by Miyamoto unfortunately is not suitable to reveal that uric acid levels might have an effect on blood pressure.

Thus, as will be further discussed below, the control of uric acid levels as a method of lowering blood pressure is not inherent by Miyamoto's flawed study conducted in a specific model system unaffected by uric acid levels. There is no realization by Miyamoto that uric acid levels are an important causal factor for

hypertension, much less that uric acid levels should be reduced to below a predefined level.

The Applicants developed a model to study the effects of uric acid on hypertension and monitored such effects over a period of weeks. See FIG 3A of the subject application. The inventors realized that in order to study the effects of uric acid in rats they needed to inhibit the activity of uricase, an enzyme in rats but not in humans that breaks down uric acid. This led to the development of the oxonic rat model involving the administration of oxonic acid to inhibit uricase. Using this new model system, the Applicants demonstrated for the first time that lowering uric acid produced a drop in blood pressure. The inventors' discovery has since been confirmed in human experiments wherein a decrease in blood pressure is directly associated with an intentional reduction of uric acid levels in patients. (See paragraphs 10 and 11 of Johnson Declaration).

Applicants primary discovery is that hypertension can be treated by reducing uric acid levels. It is practically indisputable that inhibition of xanthine oxidase results in reducing uric acid levels. Accordingly, Applicants respectfully assert that the administration of xanthine oxidase inhibitors, as a general class to reduce uric acid levels, is fully enabled. Applicants respectfully request reconsideration of this 35 USC § 112, first paragraph, rejection.

Next, cancelled claims 1, 5, 7 and 14 were rejected under 35 USC § 102 as being anticipated by Miyamoto et al. Applicants respectfully assert that new claims 16 and 17 obviate this rejection. Claims 16 and 17 recite that a composition is administered to reduce uric acid levels to a certain level. As noted above, Miyamoto et al. does not recognize that uric acid is even relevant to hypertension. The Miyamoto et al. paper monitored the affects of a xanthine oxidase inhibitor in a SHR rat model for a short period of time (about 1 hour) and hypothesized that it is a decrease in oxidants that affects blood pressure. However, it has been shown in later studies that any effect

observed by administering a xanthine oxidase in the SHR model is not sustained over a longer period of time. (See Johnson Declaration, paragraph 4).

Unfortunately, Miyamoto's experimental design could not have revealed the causal relationship of uric acid levels to hypertension because the SHR rat becomes hypertensive by a genetic defect and not by a uric acid mediated event (see Johnson Declaration, paragraph 5). The method of claims 16 and 17 involves the intentional reduction in uric acid to achieve a certain level. The effects of reducing uric acid in humans would necessarily require a period of xanthine oxidase inhibition longer than that to achieve a decrease in oxidants. This is because serum uric acid is regulated not only by its production, but by excretion (via the urinary and gastrointestinal tracts) and therefore, it takes a longer time to lower uric acid levels to produce a beneficial effect on hypertension. These issues are nowhere contemplated or addressed by the Miyamoto et al. paper.

To summarize, the intentional reduction of uric acid in humans is not taught or suggested by the Miyamoto et al. paper. Furthermore, Miyamoto et al.'s study in the SHR rat which fails to contemplate the effects of uric acid does not inherently anticipate the intentional reduction of uric acid in humans, much less the reduction of uric acid below a specified level. Accordingly, the Miyamoto et al. paper cannot anticipate claim 16 and 17. Applicants respectfully request reconsideration of this under 35 USC § 102 rejection.

Cancelled claims 1, 5, 7 and 14 were rejected under 35 USC § 102 as being anticipated by Baldwin (US 4,058,614). Applicants respectfully assert that new claims 16 and 17 obviate this rejection. Baldwin teaches a new class of substituted imidazole compounds and teaches that certain imidazole compounds are useful as xanthine oxidase inhibitors whereas others are useful as anti-hypertensive agents. Baldwin stresses that certain compounds of the class are useful as either an anti-hypertensive agent or as a xanthine oxidase inhibitor. See Col. 1, lines 10-20.

It is clear from the straightforward teachings of Baldwin that there is no contemplation or recognition that reducing uric acid levels would have a beneficial affect on blood pressure. Indeed, Baldwin teaches that the way to determine which compounds have antihypertensive activity is by testing them in the SHR rat model. See Column 6, lines 50-57 of the Baldwin patent. As already discussed above concerning the Miyamoto paper, if the SHR rat model is used to test whether certain compounds have antihypertensive activity, clearly such activity is not mediated by a uric acid related event since this model is not suitable to observe uric acid mediated hypertension.

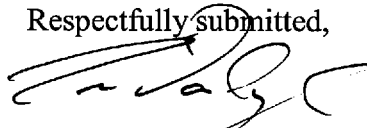
Incidentally, imidazole compounds have been well characterized to mediate anti-hypertensive effects by a variety of mechanisms, including via inhibiting adrenal function, blocking beta adrenergic receptors, stimulating central alpha 2 adrenergic receptors, or by blocking angiotensin II receptors (Johnson Declaration, paragraphs 12-14). The anti-hypertensive effects observed by certain imidazole compounds by testing in the SHR rat as taught by Baldwin is in all likelihood mediated by one of these mechanisms.

Given Baldwin's emphasis that certain compounds either serve as anti-hypertensives or xanthine oxidase inhibitors, it is reasonable to assert that Baldwin actually teaches away from reducing uric acid levels as a methodology for treating hypertension. At a minimum, the Baldwin patent does not suggest administering a xanthine oxidase inhibitor as a treatment for hypertension. Furthermore, there is no suggestion that any dosage of a xanthine oxidase inhibitor should be given to treat hypertension. Without question, there is no suggestion in Baldwin to administer a therapeutically effective amount of a composition comprising a xanthine oxidase inhibitor in order to reduce uric acid in a patient to achieve a level of 4 to 6 mg/dl. Without such teaching or suggestion, the Baldwin patent does not anticipate, either explicitly or inherently, claims 16 or 17.

Applicant asserts that all grounds for rejection of the pending claims are addressed and obviated. It is respectfully urged that this application is in condition for

allowance. Applicants request that the Examiner call the undersigned if clarification is needed on any aspect of this Reply, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Timothy H. Van Dyke', with a stylized flourish at the end.

Timothy H. Van Dyke

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Kantamneni, Shobha
Art Unit : 1617
Applicants : Kivlighn et al.
Serial No. : 09/892,505
Filed : June 28, 2001
For : Treatment For Cardiovascular Disease

DECLARATION OF RICHARD JOHNSON, M.D.

I, Richard Johnson. hereby declare and say as follows:

THAT, I am employed as a Professor of Medicine at the University of Florida, Gainesville, FL.;

THAT, I am one of the above-named Applicants and inventors of the subject matter described and claimed in the above-identified patent application;

THAT, by virtue of my educational and employment background, my attendance at seminars, my ongoing research, my continuing review of scientific periodicals and journals, and through correspondence with professional colleagues, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension;

THAT, I have studied the application Serial No. 09/892,505 and office actions which have been issued during prosecution of this application (including cited references), as well as responses which have been filed on the Applicants' behalf, and being thus duly qualified declare as follows:

1. The Examiner has raised the issue that the claims are not enabled for the use of all xanthine oxidase inhibitors. In my opinion, the wording in new claim 16 avoids any issues of enablement. Our primary discovery is that elevated uric acid is a causal factor associated with hypertension. The new claim 16 is restructured to emphasize that hypertension is treated by reducing uric acid. The step of reducing uric acid pertains to the administration of a composition comprising a xanthine oxidase inhibitor. Uric acid is

formed by the oxidation of xanthine by xanthine oxidase. Thus, any enzyme that inhibits xanthine oxidase will, per se, reduce uric acid levels in a patient.

2. The Examiner cites to the Miyamoto et al. paper for the proposition that the ability of xanthine oxidase inhibitors to lower blood pressure is unpredictable. However, when carefully examining the Miyamoto et al. paper it is apparent that the variability can be explained by Miyamoto's misguided focus on the production of oxidants without any consideration of the role of uric acid in conjunction with utilizing a flawed SHR rat model. First, it is important to point out that Miyamoto never considered the possibility that xanthine oxidase inhibitors might act by lowering uric acid. Rather, the authors attributed the effect of xanthine oxidase inhibitors to lower blood pressure due to their ability to lower oxidants. However, unlike the uniform lowering of uric acid by xanthine oxidase inhibitors, the effect of xanthine inhibitors on lowering oxidants is variable because some xanthine oxidase inhibitors, such as allopurinol, act by competing with the substrate, xanthine. As such, allopurinol will be converted to alloxanthine, releasing superoxide in the process. Thus, this drug will reduce uric acid formation but will have only minimal effect to block superoxide formation [1]. Only noncompetitive xanthine oxidase inhibitors will block both superoxide and uric acid generation.

3. I agree with Miyamoto's position that any effects on blood pressure that Miyamoto was able to observe were due to the inhibition of oxidants as opposed to lowering uric acid. This is evident from the fact that the effects were observed within minutes (about 60 min), and lowering systemic uric acid levels requires 24 to 48 hours since uric acid has a long half life in humans, and in order to see a decrease one must not simply block generation but also wait for excretion [2]. In contrast, oxidants such as superoxide have a very short half life, so blocking xanthine oxidase would result in an immediate reduction in xanthine oxidase derived oxidants. Indeed, the marked variability in the reported studies is consistent with the variable effects of these inhibitors on suppressing oxidants; for example, allopurinol was found to be the least protective [1]

4. In contravention to Miyamoto et al.'s misunderstanding that xanthine oxidase inhibitors might be useful in the treatment of hypertension through an antioxidant mechanism, additional studies have shown that the effect of xanthine oxidase inhibition in the SHR rat is not sustained over longer periods of time. Indeed, several studies have reported no effect on blood pressure in the SHR rat when evaluated over days [3-5, *but see* 6 (tungsten poisoning with prolonged effect).].

5. One might raise the question that if lowering uric acid should reduce blood pressure in patients with essential hypertension, then why did it fail in the SHR rat. The problem with the SHR rat is that it does not replicate how hypertension develops in man. Thus, our studies have strongly suggested that hypertension in humans occurs via two phases, an initial phase mediated by renal vasoconstriction, and a second phase in which intrarenal arteriolar disease develops that causes a persistent salt-sensitive hypertension [7, 8]. In contrast, hypertension in the SHR rat is due to a hereditary reduction in the afferent arteriolar lumen [9]. Since hypertension in the SHR rat is due to a hereditary (or congenital) mechanism, uric acid levels are not consistently elevated in this model nor should one expect that lowering uric acid would be beneficial

6. The inability of xanthine oxidase inhibitors to chronically lower BP through the oxidant pathway as proposed by Miyamoto also should negate their paper as providing prior art of the effectiveness of this class of drugs in human hypertension. The inability of xanthine oxidase inhibition to lower blood pressure via its antioxidant effects is not surprising, as most studies suggest that the principle oxidants driving hypertension are derived from a separate enzyme system, termed the NADPH oxidase system [10]. Furthermore, and sadly, while some small trials have shown some positive effects, the results of large clinical trials examining the effect of antioxidants in lowering blood pressure have been disappointing [11].

7. Since many authorities had viewed the SHR rat as a good model of human hypertension, the lack of long-term blood pressure lowering with xanthine oxidase inhibitors, coupled with the lack of effect of antioxidants in general, steered people away

from using these agents to treat hypertension. Indeed, some even argued that to lower uric acid might be bad, since uric acid is an antioxidant [12, 13].

8. It was in this setting that we performed our studies. Specifically, we found that raising uric acid in rats resulted several weeks later in the development of hypertension, and we later showed that this was due to an acute effect to block endothelial function and later by causing renal microvascular disease [8, 14, 15]. We realized that in order to study the effects of uric acid in rats we needed to inhibit the activity of uricase, an enzyme in rats but not in humans that breaks down uric acid. This led to the development of the oxonic rat model involving the administration of oxonic acid to inhibit uricase. Using this new model system, we were able to demonstrate for the first time that elevating uric acid led to development of hypertension and lowering uric acid could treat the hypertension. Moreover, we discovered that lowering uric acid with two agents of different classes (uricosuric and xanthine oxidase inhibitors) could treat the hypertension [14]. Since the only action in common with these two drugs is to lower uric acid, the finding that both could lower blood pressure strongly supported the role of uric acid in mediating the hypertension.

9. We have since showed that an elevated uric acid is present in the vast majority (89%) of adolescents with new onset essential hypertension as opposed to other types of hypertension or compared to normals, and that the relationship of uric acid with hypertension was linear [16]. Hence, further lowering uric acid might result in a lowering of blood pressure regardless of the initial uric acid value.

10. We also performed the first study in humans to show that allopurinol can lower blood pressure in essential hypertension [17]. Interestingly, the ability of allopurinol to lower blood pressure has recently been confirmed in a prospective trial in subjects with chronic kidney disease and asymptomatic hyperuricemia [18]. However, it must also be remembered that no antihypertensive has yet to be proven uniformly effective at lowering blood pressure; indeed, in most studies only 60% of subjects will respond to any single drug [19].

11. There are now several published studies which are confirming our discovery that uric acid has a causal role for hypertension. The Framingham Heart Study Group, who in 2000 wrote in a published exchange with me that there is no evidence that uric acid is a cardiovascular risk factor [20, 21] have subsequently rescinded and acknowledged that their data now fits with our hypothesis [22]. Indeed, I was invited to write the accompanying editorial that summarized the now convincing evidence that uric acid is a true risk factor for hypertension [23]. Other recent papers have also come to the same conclusion and acknowledge our leadership in first identifying this association [24].

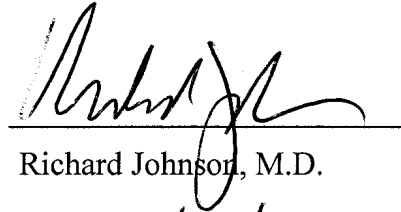
12. I have reviewed the Baldwin patent which teaches a broad class of substituted imidazoles wherein the members of the class either lower blood pressure or block xanthine oxidase. Interestingly, nowhere in the patent do they claim that blocking xanthine oxidase lowers blood pressure. There is also no mention made of the necessity to follow uric acid levels in order to obtain an effect.

13. In contrast, Baldwin teaches that the way to determine which of their compounds have antihypertensive activity is by testing them in the SHR rat model. See Column 6, lines 50-57 of the Baldwin patent. In view of Baldwin's use of the SHR rat model to test whether certain compounds of the class have antihypertensive activity, any such activity can not be mediated by a uric acid related event. As I have explained above, the SHR rat model is not suitable to observe uric acid mediated hypertension.

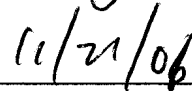
14. Incidentally, imidazole compounds have been well characterized to mediate anti-hypertensive effects via a number of mechanisms, including inhibiting adrenal function, stimulating central alpha 2 receptors, blocking beta adrenergic receptors or by blocking angiotensin II receptors [25-27]. In my opinion, the anti-hypertensive effects observed by certain imidazole compounds by testing in the SHR rat as taught by Baldwin is in all likelihood mediated by one of these mechanisms.

15. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under ' 1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.



Richard Johnson, M.D.



Date

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